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Lung Biopsy Findings in Transposition of the Great Arteries With Ventricular Septal Defect: Potentially Reversible Pulmonary Vascular Disease Is Not Always Synonymous With Operability

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Pulmonary vascular structure was analyzed in lung biopsy specimens taken from 28 children, aged 2 months to 15 years, with transposition of the great arteries and ventricular septal defect. Cellular intimal proliferation occurred in infants as young as 2 months, but it increased markedly between ages 7 to 9 and 10 to 12 months, and the increased obstruction was associated with a lower mean percent arterial medial thickness in patients older than 10 months than was found in younger patients. Early generalized arterial dilation appeared without the intimal fibrosis and dilation lesions characteristic of classical grade III and IV pulmonary vascular disease. Intimal abnormalities increased with age and pulmonary artery pressure, but mean percent arterial medial thickness was inversely related to mean pulmonary artery pressure ($r = -0.5$; $p < 0.0001$).

Nine patients survived intracardiac repair and six did not. Five of the patients who died were of similar age (12 months or less), had similar preoperative hemodynamic and pulmonary vascular abnormalities compared with the survivors and died after a clinical course compatible with pulmonary vascular disease. The findings emphasize that potential structural reversibility is not synonymous with "operability." Further studies are indicated on the function of the excessively muscularized pulmonary vascular bed of such infants.

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In patients with transposition of the great arteries and ventricular septal defect, pulmonary vascular disease appears in early infancy and develops rapidly; 75% of such patients older than 1 year are said to have grade IV pulmonary vascular disease (1–3). In 1974 Newfeld et al. (1) reported that in transposition with ventricular septal defect the Heath-Edwards grade (2) of pulmonary vascular disease increased as the mean pulmonary artery pressure increased, and a mean pressure greater than 50 mm Hg in patients older than 1 year was generally associated with grade IV disease. These authors also noted that pulmonary vascular resistance calculated using the Fick method of determining pulmonary blood flow could underestimate the severity of pulmonary vascular disease.

The present report describes the pulmonary vascular structure in lung biopsy specimens taken from 28 children with transposition of the great arteries and ventricular septal defect, a series that includes examples of all grades of pulmonary vascular disease. Descriptive and quantitative pathologic techniques were used and the structural findings were related to the hemodynamic findings at cardiac catheterization, patient management and the outcome of intracardiac repair.

Methods

Study patients. Pulmonary vascular structure was studied in lung biopsy specimens taken from 28 children, aged 2 months to 15 years, with transposition of the great arteries and ventricular septal defect (Table 1). All patients had severe pulmonary hypertension, and in 96% the mean pulmonary artery pressure was 40 mm Hg or more. Three patients had a patent ductus arteriosus. None had Down's syndrome. Nine patients survived an intracardiac repair (arterial switch operation in three and Mustard or Senning operation with closure of ventricular septal defect in six). Six patients died during or soon after repair and in five the clinical course was compatible with a diagnosis of pulmonary vascular disease. A palliative arterial switch or Mustard

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Table 1. Summary of Clinical and Pathologic Findings in 28 Cases

Age Range	No. of Patients	$\overline{PAP}$ (mm Hg)	Pulmonary Vascular Changes %AMT	Pulmonary Vascular Changes Grade PVD
2 to 3 mo	2	62 to 65	23.1%	I
4 to 6 mo	6	40 ± 7.5	21.3%	I/II
7 to 12 mo	6	47 ± 8.6	21.9% at 7 to 9 mo	I/II
			8.8% at 10 to 12 mo	III
1.3 to 3 yr	5	56 ± 4.9	8.1% at 1 to 2 yr	III
			5.2% at 2.1 to 3 yr	III
3.5 to 15 yr	9	68 ± 6.0	6.5% at 3.1 to 8 yr	III/IV
			9.7% at 15 yr (n = 1)	III/IV

%AMT = mean percent arterial medial thickness in arteries 50 to 100 μm in diameter; Grade PVD = Heath-Edwards (2) grade of pulmonary vascular disease; $\overline{PAP}$ = mean pulmonary artery pressure.

procedure was performed in eight cases. Two patients will have an intracardiac repair and three were deemed inoperable and have not yet had palliative surgery. The lung biopsy specimens were taken at the time of intracardiac surgery, which was corrective or palliative in 13 patients and performed electively for diagnostic purposes in 15. The mean interval between cardiac catheterization and lung biopsy was 2 weeks.

Pathologic Studies

The lung biopsy specimen was taken from the anterior segment of the left upper lobe or the apical segment of the left lower lobe, with the airways distended and fixed in inflation. Four micron sections of paraffin-embedded tissue (average size 2 × 1 cm) were stained with hematoxylin-eosin, Miller's elastic stain counterstained with van Gieson's stain, and Perls' stain for iron.

Descriptive studies. The appearance of arteries accompanying preacinar airways, terminal bronchioli, respiratory bronchioli and alveolar ducts and those lying within the alveolar walls was described separately, noting medial hypertrophy and the presence and severity of any intimal proliferation and fibrosis, abnormal dilation and dilation lesions. In addition, the overall appearance of the structural abnormalities was graded according to the Heath-Edwards classification (2). In the veins, wall thickness, the development of an external elastic lamina ("arterialization") and the presence of any intimal fibrosis were noted.

Quantitative studies and analysis of data. In each biopsy specimen, a mean of 35 arteries were measured (range 20 to 55). In each case, pulmonary artery muscularity was assessed by determining the percent arterial medial thickness of all arteries examined and calculating the mean percent in arteries grouped according to external diameter (1 to 50, 51 to 100, 101 to 200 μm, and so on) (4). In each case percent arterial medial thickness in arteries of different size ranges was compared with the normal value (5) for age using nonorthogonal analysis of variance. Using multiple linear regression analysis the mean percent arterial medial thickness in arteries of different size groups was related to age and pulmonary artery mean pressure.

To determine whether muscle had differentiated in more peripheral arterial vessels than is normal (extension), the proportion of muscular, partially muscular and nonmuscular arteries was determined in vessels accompanying terminal and respiratory bronchioli and alveolar ducts, and the results were compared with the normal values for age (5). In each case, the external diameter of arteries accompanying each type of peripheral airway was determined and the mean external diameter was calculated and compared with the normal for age using Student's t test (5). The number of patient intraacinar arteries was determined by counting the number of arteries and alveoli within the same lung field, using as many fields as possible and calculating the ratio of arteries to alveoli to compensate for differences in the degree of inflation in different lungs (5). The alveolar/arterial ratio was not determined in specimens showing generalized arterial dilation.

Results

Descriptive Studies

The lung biopsy specimens from the five youngest patients, aged 2 to 4 months, all showed a marked increase in muscularity in the preacinar, terminal and respiratory bronchiolar arteries with extension of muscle into the alveolar duct and alveolar wall vessels. Despite the extension of muscle, there was a marked discrepancy in wall thickness between terminal and respiratory bronchiolar arteries, which showed severe medial hypertrophy, and more peripheral

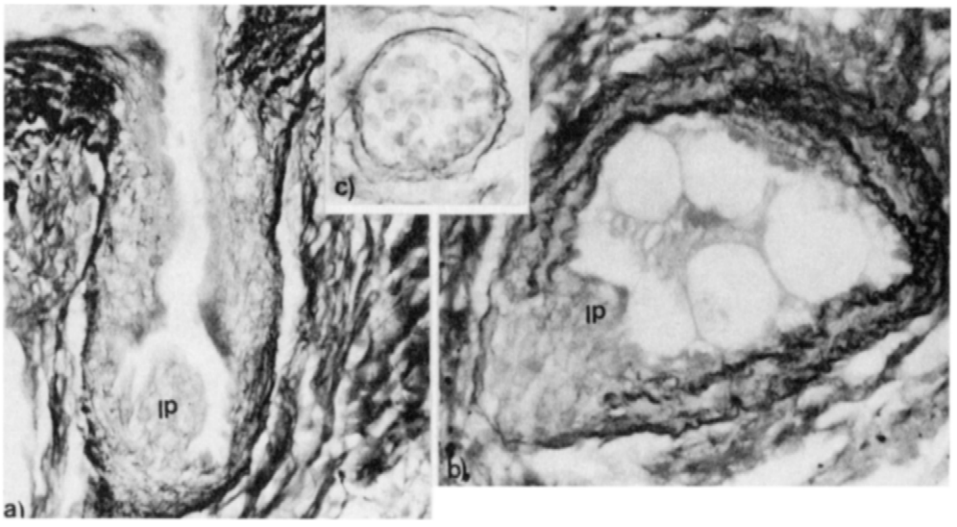

Figure 1. Case 10. Photomicrographs from a lung biopsy specimen from a child aged 2 months showing (**a**) cellular intimal proliferation (IP) in a branch arising from a preacinar muscular artery; (**b**) a respiratory bronchiolar artery with intimal proliferation; and (**c**) a partially muscularized alveolar duct artery. Original magnification × 500 (**a**), 788 (**b**), 770 (**c**), all reduced by 40%.

arteries, which did not. Small amounts of cellular intimal proliferation were present in the preacinar, terminal and respiratory bronchiolar arteries in three of the five patients including the 2 month old infant (Fig. 1). In the seven patients aged 5 to 9 months, pulmonary vascular abnormalities were more severe. Intimal proliferation, usually associated with some fibrosis, occurred in five patients and in the patients aged 7 months or older the alveolar duct and alveolar wall arteries were thin-walled and dilated, although the majority of these vessels were still inappropriately muscularized. Thus, all patients aged less than 9 months had grade I or II pulmonary vascular disease (2).

The lung biopsy specimens from the two patients aged 10 and 12 months had medial hypertrophy with severe intimal proliferation and some fibrosis in preacinar, terminal and respiratory bronchiolar arteries and more thin-walled arteries beyond (Fig. 2). These patients had grade III pulmonary vascular disease. Of the 14 patients aged 19 months or older only 1, aged 19 months, had minimal disease with only a small amount of cellular intimal proliferation. The remaining patients had severe preacinar intimal fibrosis with proliferation, atrophy of the underlying media, sometimes associated with capillary recanalization, thin-walled dilated intraacinar arteries and hyalinization of the arterial wall with plexiform lesions (n = 4), changes compatible with grade III (n = 7) and grade IV (n = 6) pulmonary vascular disease (Fig. 3) (2). The youngest patient in whom plexiform lesions were present was aged 3.5 years.

In all patients older than 4 months, both pre- and intraacinar veins showed a slight increase in wall thickness with formation of an external elastic lamina in some of the intraacinar vessels. The changes were invariably mild and no patient showed venous intimal fibrosis. Small amounts of iron were deposited in the arterial walls of only two

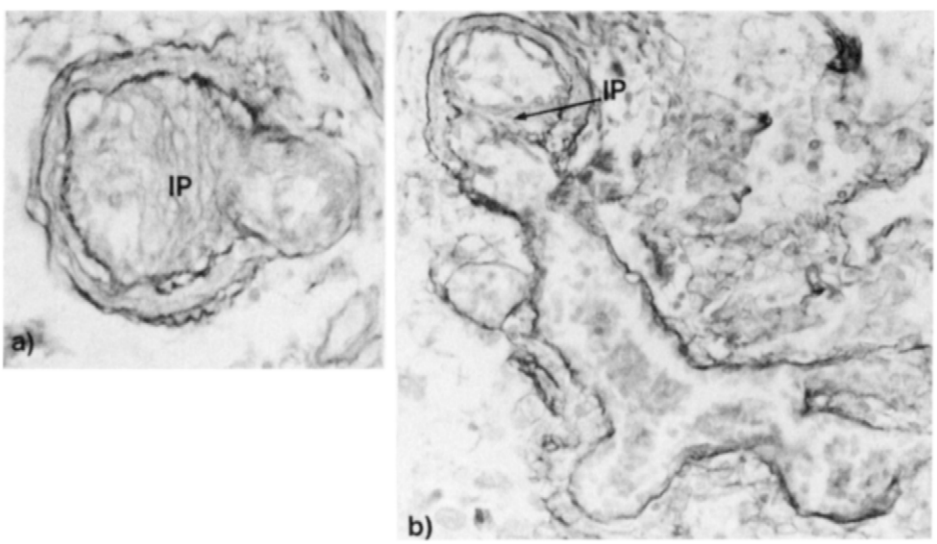

Figure 2. Case 15. Photomicrographs of a lung biopsy specimen from a child aged 12 months showing (**a**) a respiratory bronchiolar artery with intimal proliferation (IP); and (**b**) a respiratory bronchiolar artery with intimal proliferation in its thin-walled branches (**arrow**). Original magnification × 716 (**a**) and × 750 (**b**), both reduced by 35%.

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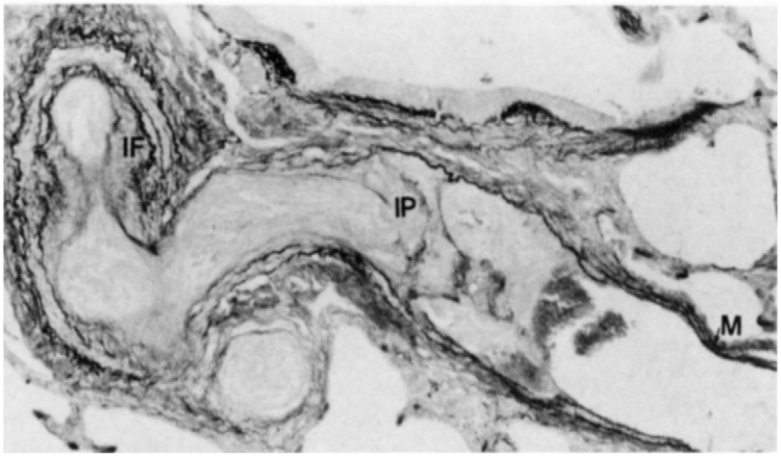


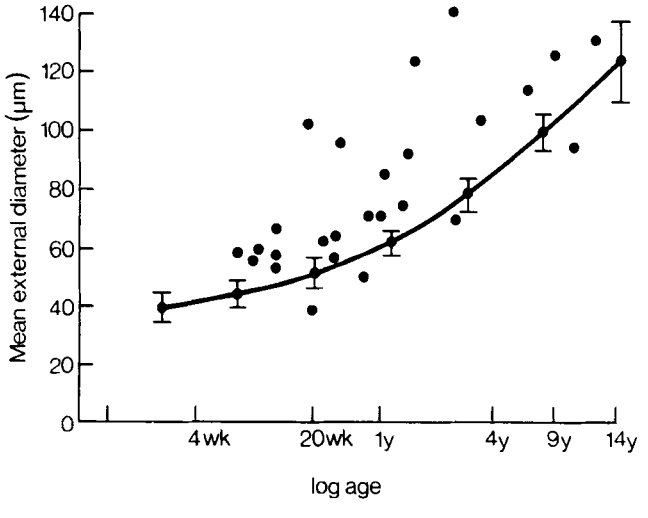
Figure 3. Case 18. Photomicrographs of a lung biopsy specimen from a child aged 3.5 years showing a terminal bronchiolar artery with intimal fibrosis (IF) and cellular intimal proliferation (IP) obstructing the lumen of the vessel and one of its branches. Distal to the obstruction the media (M) is extremely thin. Original magnification × 192, reduced by 35%.

patients, aged 3 and 7 years, respectively, but siderophages were present in these and in another seven patients, the youngest being 6 months of age.

Quantitative Studies

Mean percent arterial medial thickness was significantly greater than normal for age in 19 patients ($p < 0.0001$) and normal or even below normal in the remaining 9 patients, who were generally aged over 10 to 12 months. Muscularity decreased abruptly in arteries 50 to 100 μm in diameter between the ages of 7 to 9 and 10 to 12 months (Table 1), when obstructive intimal proliferation was seen in larger, more proximal preacinar and terminal bronchiolar arteries. Mean percent arterial medial thickness also decreased with increasing mean pulmonary artery pressure ($r = -0.5$; $p < 0.0001$). Abnormal extension of muscle along the arterial pathway occurred in 75% of patients aged less than 7 months but not in the older children, except for one child aged 1 year.

Figure 4. Mean external diameter (μm) in arteries accompanying respiratory bronchioli in 26 children with transposition of the great arteries and ventricular septal defect, plotted against the cubic polynomial expressing the relation between size and log age in normal children; shown as a continuous line with upper and lower confidence limits of the mean. (Accurate measurements could not be made in two cases.)



The mean external diameter of arteries accompanying each type of peripheral airway was generally normal or even greater than normal for age, as shown for the arteries accompanying respiratory bronchioli in Figure 4. The alveolar/arterial ratio, expressing the number of intraacinar arteries, exceeded the normal upper limit of 10 in seven cases but was greater than 12 in only two (5).

Pulmonary vascular structure in relation to outcome. Table 2 shows that six of the nine patients who survived an intracardiac repair were aged 9 months or less. Biopsy specimens from these six patients showed an increase in preacinar arterial muscularity in all, an increase in intraacinar arterial muscularity in most, and a mean arterial pressure of 40 mm Hg or more in all but one patient. Biopsy specimens from the three older survivors showed a less marked increase in intraacinar arterial muscularity, and two showed intimal fibrosis rather than cellular proliferation in the preacinar vessels. The patient with the lowest value for mean percent arterial medial thickness (Case 7, Table 2) had severe pulmonary hypertension immediately after the intracardiac repair.

The six patients who died during repair were of similar age, 12 months old or less, and had pulmonary vascular abnormalities that were similar to those found in the survivors. Of these six patients, five died within 24 hours of operation after a clinical course compatible with a diagnosis of pulmonary vascular disease (the pulmonary artery pressure was not monitored). The systolic pulmonary artery pressure at the end of the operation was less than 30 mm Hg in the survivors and greater than 40 mm Hg in the five patients who died with pulmonary vascular disease. The sixth patient died because of a massive gastrointestinal hemorrhage on the third postoperative day, without evidence of

Table 2. Hemodynamic and Structural Data in 23 Cases in Relation to Management and Outcome of Intracardiac Repair

Case	Age (mo)	Operation	Preoperative $\overline{PAP}$ (mm Hg)	%AMT	Arterial Appearance		Grade PVD
					Preacinar	Intraacinar	
Patients Who Survived Intracardiac Repair							
1	4	SW	28	20	M ↑	M ↑ IP†	I
2	5	M	40	16	M ↑ IP	M ↑	II
3	6	M	52	14	M ↑ IF	M ↑	II
4	6	S	40	31	M ↑	M ↑	I
5	7	M	51	33	M ↑ IP	M ↑ IP†	II
6	9	M	45	16	M ↑ IP	M ↑ IP†	I
7	10	S	48	4*	M ↑ IF	M ↑ IP†	III
8	19	SW	50	11	M ↑ IP	M ↑	II
9	36	SW	52	7	M ↑ IF	M ↑ IP†	III
Patients Who Died at Intracardiac Repair							
10	2	SW	65	16	M ↑ IPs	M ↑	I
11	3	M	62	31	M ↑ IPs	M ↑	I
12	4	SW	40	24	M ↑	M ↑	I
13	4	SW (GIH)	40	16	M ↑	M ↑	I
14	7	SW	50	22	M ↑ IP	M ↑	I
15	12	M	58	14	M ↑	M ↑	III
Patients Who Had Palliative Intracardiac Surgery							
16	15	M	60	9	M ↑ IF	M ↓	III
17	19	M	60	5	M ↑ IF	M ↓	III
18	42	SW	69	6	M ↑ IF	M ↓ pl	IV
19	96	SW	68	6	M ↑ IFplex	M ↓ occ	IV
20	108	M	68	10	M ↑ IFplex	M ↓	IV
21	122	M	40	11	—	M ↓ occ	IV
22	148	S	58	6	M ↑ IF	M ↓ occ	IV
23	180	S	65	10	M ↑ IF	M ↓ occ	III

Note: An additional five patients await corrective or palliative surgery. *Immediately after repair pulmonary artery pressure 60/40 and systemic arterial pressure 85/60 mm Hg.; †proliferation in respiratory bronchiolar arteries. GIH = gastrointestinal hemorrhage; IF = intimal fibrosis; IP = intimal proliferation; IPs = slight amount of intimal proliferation; M ↑, M↖, M ↓ = pulmonary artery muscularity increased, not increased significantly and reduced, respectively; M = Mustard operation; occ = arteries occluded by fibrosis; pl = plexiform lesions; S = Senning repair; SW = arterial switch repair; other abbreviations as in Table 1.

pulmonary hypertension. Only one patient who died had pulmonary vascular disease greater than grade I. All lung biopsy specimens from patients who had a palliative operation showed severe obstructive pulmonary vascular disease of grade III or IV.

Discussion

Pathologic features. Intimal proliferation in our cases of transposition of the great arteries and ventricular septal defect was found in lung biopsy specimens from infants as young as 2 months of age, and the severity of intimal abnormalities increased with age and pulmonary artery pressure, as has previously been reported (1,6). In the present study, however, the pathologic abnormalities were generally less severe in type during the first year of life than has previously been reported (1). Exuberant cellular intimal proliferation rather than intimal fibrosis was the dominant feature and all patients aged less than 9 months had only grade I or II pulmonary vascular disease. Other workers (6) recently found intimal proliferation rather than fibrosis in 10 patients with transposition and ventricular septal defect who were less than 4 years of age. Our patients showed a considerable amount of obstructive cellular intimal proliferation and the majority of those older than 9 months had dilated alveolar duct and alveolar wall arteries in which mean percent arterial medial thickness showed little if any increase. These patients were developing early generalized dilation without the marked intimal fibrosis characteristic of late grade III and IV pulmonary vascular disease.

The findings are unlike those seen in children with an isolated ventricular septal defect. In such children, lung biopsy specimens may show peripheral arterial dilation with a normal mean percent arterial medial thickness in the presence of severe intimal fibrosis in more proximal vessels, but these specimens are usually from children who are at least 10 years old. In children with both transposition and ventricular septal defect, however, obstructive cellular in-

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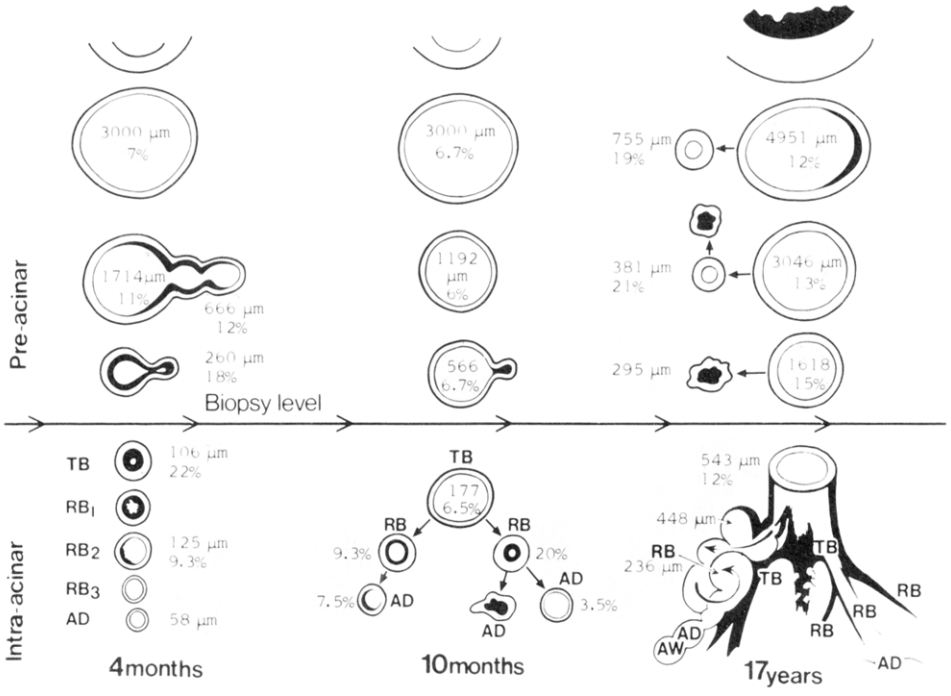

Figure 5. Diagrams of serial reconstructions of the pulmonary artery pathways in three previously reported (7) cases of transposition with ventricular septal defect from the preacinar to terminal bronchiolar (TB), successive generations of respiratory bronchiolar (RB_1, RB_2, RB_3) and alveolar duct (AD) arteries. External diameter and percent medial thickness of arteries are shown. **Black areas** within the lumen indicate intimal proliferation and fibrosis. AW = alveolar wall. (Reproduced with permission from Haworth SG [7].)

timal proliferation is present before significant fibrosis has had time to develop. These observations emphasize the difficulties inherent in applying a rigid classification scheme to pulmonary vascular disease irrespective of age and etiology. Our present findings in lung biopsy specimens are supported by a previous study of autopsy specimens (7), in which serial reconstructions were made of arterial pathways. In the infants with transposition and ventricular septal defect in that study, pulmonary hypertension with an elevated resistance was associated with severe cellular intimal proliferation, strategically placed at the end of each arterial pathway to obstruct the flow of blood into the acinus, and not with obliterative pulmonary vascular disease of grade IV severity or more.

Unlike previous workers (1) we did not find plexiform lesions in children younger than 3.5 years, probably because we examined only biopsy tissue. Plexiform lesions are not associated with all muscular pulmonary arteries and therefore are not invariably present in lung biopsy specimens. They can occur in very young patients.

Hemodynamic correlations. The type of intimal disease found in our study was less severe than that previously reported (1) and the correlations between structure and hemodynamic findings were also different. In our series, all but 1 of the 14 patients older than 1 year had a mean pulmonary artery pressure of at least 50 mm Hg, but 5 of the 14 did not have the pulmonary vascular disease of grade IV severity reported by others (1). However, because 96% of the patients in the previous series were examined at autopsy they may have been more severely affected than our patients. In addition, unlike Yamaki and Wagenwoort (6), we found a negative correlation between pulmonary artery pressure and muscularity. The difference is readily explained. Their study was done on autopsy tissue, but the arteries were not landmarked according to their accompanying airway. In an autopsy study, the majority of arteries studied were probably proximal to those arteries (50 to 100 μm in diameter) whose wall thickness was determined in our study. Recent autopsy studies (5,7) of patients with transposition and ventricular septal defect have demonstrated a progressive increase in medial hypertrophy in small preacinar and terminal bronchiolar arteries whereas wall thickness decreases in more peripheral vessels as obstructive intimal proliferation and fibrosis develop (Fig. 5).

The intraacinar arteries were normal or even larger than normal for age in nearly all of our patients. These results are difficult to assess because in patients older than 9 months, and possibly even younger patients these arteries appeared to be dilated. Previous studies on children with pulmonary hypertension have reported a reduction in intraacinar arterial size, but the altered vessels have generally been extremely thick-walled and the patients have usually been young children with an isolated ventricular septal defect (8,9). Similarly, the present series did not demonstrate the reduction in number of intraacinar arteries previously associated with pulmonary hypertension in young children (8,9). However, the tortuosity of the relatively thin-walled intraacinar vessels seen in many patients with transposition and ventricular septal defect could have increased the number of vessels seen in any cross-sectional area of lung tissue and, as a result, spuriously increased arterial number. In the present study, obvious occlusion of alveolar duct and alveolar wall

arteries by intimal fibrosis was evident in lung biopsy specimens from six patients aged 7 years or more.

Surgical correlations. The preoperative lung biopsy specimens from patients who survived an intracardiac repair showed severe medial hypertrophy of both preacinar and, generally, of intraacinar vessels with or without intimal proliferation in those aged 9 months or less. The three oldest patients who survived had more advanced changes, and one who had considerably reduced intracardiac arterial muscularity had pulmonary hypertension immediately after the repair. However, other studies (10,11), in which lung biopsy was performed before and some time after pulmonary artery banding, suggest that all of our patients had potentially reversible pulmonary vascular disease.

Five patients who died at operation were thought to have died of pulmonary vascular disease. They had structural abnormalities similar to those of patients who survived, and might have been expected to fare even better because most had medial hypertrophy with little if any intimal proliferation. These findings indicate that potential reversibility of pathologic lesions is not synonymous with "operability." The reasons for this are not clear. Lung tissue from our patients who died showed severe pulmonary artery medial hypertrophy, and this may predispose to excessive lability of the pulmonary circulation and to pulmonary hypertensive crises (12). In the systemic circulation, however, excessive muscularity is associated with a reduction in contractility (13). In the lung, excessive contractility may be a transitory feature of the immature pulmonary circulation. Recent studies (14) have shown that the smooth muscle cells of the pig lung are immature at birth and only gradually, during the first months of life, do the smooth muscle cell organelles become more contractile than secretory in type.

Therapeutic implications. Because patients who have potentially reversible pulmonary vascular disease are dying during intracardiac repair and because we have no effective specific pulmonary vasodilator drug, other strategies should be considered. Perhaps we should consider using membrane oxygenators while normalizing cardiovascular function and optimizing the environment in which the pulmonary vasculature might be expected to recover. Membrane oxygenators have been used extensively in newborn infants with respiratory distress to "buy time" for the lung to produce surfactant and the airways to recover (15). More recently, they have been used to good effect in older patients with cardiogenic shock (16). Perhaps the same principle might be applied to treatment of the pulmonary vasculature. Such supportive therapy might also facilitate intracardiac repair in patients with slightly more advanced disease whose clinical state might otherwise be left to deteriorate until the question of a heart-lung transplant arises.

Conclusion. Lung biopsy is helpful in the management of patients with transposition of the great arteries and ventricular septal defect, but the biopsy should be sufficiently deep to include preacinar and terminal bronchiolar arteries in which intimal proliferation first develops in early infancy. The presence of only a moderate increase in muscularity in the intraacinar vessels is associated with severe intimal proliferation in more proximal arteries; muscularity is inversely related to pulmonary artery pressure in this condition. Patients with potentially reversible pulmonary vascular disease can die after technically successful surgery. Support of the pulmonary circulation during the critical perioperative period by using a membrane oxygenator should perhaps be considered when conventional therapy and vasodilator drugs are proving inadequate.

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